UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,450	04/27/2001	William H. Frey II	83935	9084

28020 7590 06/13/2003

GRAY, PLANT, MOOTY, MOOTY & BENNETT, P.A.
P.O. BOX 2906
MINNEAPOLIS, MN 55402-0906

EXAMINER	
YOUNG, JOSEPHINE	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 06/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/844,450	FREY ET AL.	
	Examiner	Art Unit	
	Josephine Young	1623	

-- Th MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2002 and 09 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-80* is/are pending in the application.

4a) Of the above claim(s) *5-31 and 45-80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 32-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

In response to the Election/Restriction Requirement mailed October 24, 2002, Applicant's election without traverse of Group I, claims 1-44, drawn to methods to protect tissues using phosphate analogs, in Paper No. 5, transmitted via facsimile on November 25, 2002, is acknowledged. Further, Applicant's election without traverse of Species E, comprising methods of protecting a tissue comprising administering a phosphorylated compound comprising one or more of a group not categorized as a glycerol, amino acid, nucleoside or inositol, such as a hydrogen, a small alkyl group or an arachidonyl, in Paper No. 5, transmitted via facsimile on November 25, 2002, is acknowledged.

Accordingly, claims 45-80 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

In response to the Election/Restriction Requirement mailed March 10, 2003, Applicant's election without traverse of Group I, claims 1-4 and 32-44, drawn to methods of protecting tissue from oxidative stress, such as from free radicals, including heme/hydrogen peroxide and low molecular weight (LMW) inhibitor found in patients with Alzheimer's disease (AD), using a pyrophosphate analog, in Paper No. 7, transmitted via facsimile on April 9, 2003, is acknowledged.

Accordingly, claims 5-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-4 and 32-44 are linking claims and will be examined only as it pertains to the elected invention.

Specification

The disclosure is objected to because of the following informalities: Line 12 of page 1 of the specification indicates that the present application claims benefit of provisional application number 60/233,263, filed September 6, 2000. However, the Combined Declaration and Power of Attorney, mailed September 4, 2001, indicates that the present application claims benefit of provisional application number 60/230,263, filed September 6, 2000.

Appropriate correction is required.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below in In re Wands USPQ2d 14000. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention.

These factors include

(1) quantity of experimentation necessary,

(2) the amount of guidance presented,

(3) the presence or absence of working examples,

(4) the nature of the invention,

(5) the state of the prior art,

(6) the predictability of the art and

(7) the breath of the claims.

Claims 1-4 and 32-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the protection of tissue from oxidative stress induced by heme/peroxide and low molecular weight (LMW) inhibitor found in patients with Alzheimer's disease (AD), does not reasonably provide enablement the protection of all tissue types from oxidative stress not induced by free radicals or an agent that is capable of generating free radicals. Further, the specification does not reasonably provide enablement for the protection of tissue in subjects suffering from the compilation of diseases listed in claims 34-36. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With regard to factors (1) and (2) cited above, undue experimentation is required to determine which forms of oxidative stress and which tissues would be effected by the pyrophosphates for which the instant invention is applicable. There has not been provided adequate guidance in the written description for accomplishing and determining such, as only models based on oxidative stress induced by heme/peroxide and low molecular weight (LMW) inhibitor found in patients with Alzheimer's disease (AD) were assessed, out of the numerous known types of oxidative stress in the various tissues.

With regard to factors (4), (5) and (6), it is noted that there is a great deal of unpredictability in the art. For example, while certain antioxidants, such as vitamin E, are known to protect certain tissues from free radical damage, no effective agent or composition has been found for the treatment of all types of oxidative stress in all tissues. Therefore, the art at the time the invention was made fails to establish predictability with regard to the properties of the compositions needed to perform the scope of the methods as instantly claimed.

With regard to factors (3) and (7), it is noted that while there are some working examples of the protection of tissue from oxidative stress induced by heme/peroxide and low molecular weight (LMW) inhibitor found in patients with Alzheimer's disease (AD), it is not seen as sufficient to support the breath of the claims. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves. See In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Further, claims 1-4 and 34-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the protection of tissue from oxidative stress induced by heme/peroxide and low molecular weight (LMW) inhibitor found in patients with Alzheimer's disease (AD) using compounds with two or three phosphorus atoms, e.g. pyrophosphate, imidodiphosphate, adenylylimidodiphosphate, guanylimidodiphosphate and tripolyphosphate, does not reasonably provide enablement for the protection of tissue from oxidative stress induced by heme/peroxide and low molecular weight (LMW) inhibitor found in patients with Alzheimer's disease (AD) using any phosphorylated compound wherein there are more than three phosphorus atoms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

With regard to factors (1) and (2) cited above, undue experimentation is required to determine which phosphorylated compound wherein there are more than three phosphorus atoms would be useful in the protection of tissue from oxidative stress induced by heme/peroxide and

low molecular weight (LMW) inhibitor found in patients with Alzheimer's disease (AD) for which the instant invention is applicable. There has not been provided adequate guidance in the written description for accomplishing such, as only compounds with two or three phosphorus atoms were assessed, namely pyrophosphate, imidodiphosphate, adenylylimidodiphosphate, guanylimidodiphosphate and tripolyphosphate, out of the numerous phosphorylated compounds known in the art.

With regard to factors (4), (5) and (6), it is noted that there is a great deal of unpredictability in the art. For example, various di- and triphosphate analogs are known to be effective in the treatment of various physiological conditions, however, phosphorylated compounds with more than three phosphorus atoms are not known generally to be physiologically effective agents. Further, there is no discernable pattern as to which phosphorylated compound will protect tissue from oxidative stress, and in particular oxidative stress induced by heme/peroxide and low molecular weight (LMW) inhibitor found in patients with Alzheimer's disease (AD). The art at the time the invention was made fails to establish predictability with regard to the properties of the phosphorylated compounds needed to perform the methods as instantly claimed.

With regard to factors (3) and (7), it is noted that while there are some working examples of phosphorylated compounds with two or three phosphorus atoms, e.g. pyrophosphate, imidodiphosphate, adenylylimidodiphosphate, guanylimidodiphosphate and tripolyphosphate, it is not seen as sufficient to support the breath of the claims. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged

discovery, not how to find out how to use it for themselves. See In re Gardner et al. 166 USPQ 13o (CCPA 1970).

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 and 32-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "tissue component" in claim 1 renders the claims in which it appears indefinite. It is unclear as to if Applicant is referring only to muscarinic acetylcholine receptors (mAChR), receptors in general, phospholipids, etc. For example, it is unclear as to how a phosphorylated compound can protect another compound, such as a carbohydrate, etc. In the absence of the specific moieties intended to be protected as claimed, the term "tissue component" renders the claims in which it appears indefinite in all occurrences wherein Applicant fails to articulate by chemical name, structural formula or sufficiently distinct functional language, the particular moieties Applicant regards as those which will be protected by the composition of matter claimed.

In all occurrences, alphabetic variables with alternative definitions within the same claim render the claims in which such situation appears indefinite. For example, in claim 1, line 6, the variable X is limited to O, CH_2, NH or S; however, in line 13, X is defines as O, RCR^1, CR, C (n=4), CH (n=3), CH_2 (n=2), NH, N, or S. Similarly, in claim 1, line 10, n is defined as 1-900,

while in line 12, n is defined as 2-4. See also claim 4. While the variables may be construed as limiting the structure directly preceding the definition in particular, such an assumption is subject to undue interpretation.

Claims 34-36 recite limitation for the "subject". There is insufficient antecedent basis for this limitation in independent claim 4, one of the claims from which the claims depend.

Further, claims 34-36 are directed to various diseases from which a subject can suffer. However, there is insufficient antecedent basis for these limitations in independent claims 1 and 4, as the independent claims are directed to protecting tissue from oxidative stress, and not the treatment and/or prevention of any disease.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4 and 32-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over VENTERS Jr. et al., Brain Research, **1997**, *764*, 93-100 (V) in view of the MERCK INDEX, Twelfth Edition, **1996**, entries 3908 and 7135. (U).

Applicant claims methods of protecting a tissue component from oxidative stress, such as from free radicals, including heme/hydrogen peroxide and low molecular weight (LMW) inhibitor found in patients with Alzheimer's disease (AD), using a pyrophosphate analog comprising one or more of a group not categorized as a glycerol, amino acid, nucleoside or inositol, such as a hydrogen, a small alkyl group or an arachidonyl, and in particular, the pyrophosphate analogs etidronic acid and pamidronic acid. Further, Applicant claims methods using such compounds in combination with other anti-oxidants, such as bilirubin and bioflavinoids; and/or an enzyme, such as heme oxygenase, biliverdin reductase, catalase and peroxidase, or vectors that encode such enzymes; and/or heme binding protein, such as hemopexin or a lipoprotein.

VENTERS teaches that an endogenous inhibitor of antagonist binding to the muscarinic acetylcholine receptor (mAChR) prevalent in Alzheimer's disease (AD) brain contains free heme, a well-established source of oxidative stress capable of generating free radicals and causing neurotoxicity. See Abstract. VENTERS further discloses in the abstract that free radical scavengers and metal chelators blocked the activity of the endogenous AD inhibitor, as well as Heme oxygenase-1 (HO-1). Finally, VENTERS demonstrated that antioxidants, namely estrogen, vitamin E and vitamin C, protected the mAChR from irreversible inhibition by the endogenous inhibitor, and may function to protect the integrity of the mAChR in vivo and therefore have therapeutic potential in AD where free heme is a source of oxidative stress.

VENTERS does not explicitly state that pyrophosphate analogs in particular are useful in protecting tissue from oxidative stress, such as oxidative stress induced by the endogenous AD inhibitor that contains heme. Further, VENTERS does not specifically state any method using such pyrophosphate analogs in combination with other anti-oxidants, such as bilirubin and bioflavinoids; and/or an enzyme, such as heme oxygenase, biliverdin reductase, catalase and peroxidase, or vectors that encode such enzymes; and/or heme binding protein, such as hemopexin or a lipoprotein.

The MERCK INDEX states that the pyrophosphate analogs, etidronic acid and pamidronic acid, are sequestering and chelating agents. See entries 3908 and 7135.

It would have been obvious to one of ordinary skill in the art to use the chelating agents, etidronic acid and pamidronic acid, as set forth by MERCK, to protect tissue from oxidative stress induced by the endogenous AD inhibitor that contains heme, as VENTERS demonstrates that free radical scavengers and metal chelators are useful in blocking the activity of such endogenous AD inhibitor. A skilled artisan would have been motivated and have had a reasonable expectation of success to use any free radical scavengers, metal chelators, heme oxygenase or antioxidant, either alone or in combination to protect tissue from oxidative stress, as such compounds are known in the art, as per VENTERS, to have therapeutic potential in AD where free heme could be a source of oxidative stress.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

Claims 1-80 are pending. Claim 1-4 and 32-44 are rejected. Claims 5-31 and 45-80 are withdrawn. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Josephine Young whose telephone number is (703) 605-1201. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (703) 308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

JY
June 11, 2003

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600